REMARKS

Upon entry of this Amendment and Reply, claims 1-20 have been cancelled and new claims 21-63 are pending in the present application. Applicant wishes to thank the Examiner for initialing and returning Form PTO-1499.

Applicant respectfully submits that the amendment adds no new matter. Support for the new claims can be found on pages 3-12 of the specification as originally filed as well as the Figures and original claims 1-20.

Specifically, support for claim 21 can be found on page 3, line 6 through page 6, line 31. Claim 21 is based on claim 6 of the application as filed. Support for dependent claims 22-23 can be found on page 6, lines 8-31. Support for claim 24-27 can be found on page 5, lines 25-37 and page 6, lines 1-2. Support for claim 28 is found on page 8, lines 3-34, support for claims 29-30 is found on page 9, lines 14-37 and page 10, lines 1-3. Claims 31 and 32 are based on claim 11 as filed, claims 33 and 34 are based on claim 12 as filed and claims 35 and 36 are based on claim 13 as filed, support for claims 31-36 can be found on page 6, line 32 trough page 8, line2 and page 9, lines 14-37 and page 10, lines 1-27. Support for claim 37 is found on page 10, lines 31-36 and page 11, lines 1-7. Support for claim 38 is found on page 11, lines 14-20. Support for claim 39 is found on page 9, lines 6-37 and page 10, lines 1-3. Support for claim 40 is found on page 5, line 7 through page 6, line 14. Support for claim 41-43 can be found on page 11 lines 21-34. Claim 44 is based on claims 1 and 9 as originally filed and support can be found on pages 8, line 19 through page 11, line 13. Claims 45-50 depend from claim 44. Support for claim 45 is found on page 10, lines 4-26. Support for claims 46-47 can be found on page 6, lines 8-23. Support for claim 48 is found on page 8, lines 3-19. Support for claims 49-50 can be found on page 11, lines 21-33. Claim 51 corresponds to claim 2 as filed, support for claim 51 is found on page 5, line 24 through page 11, line 13. The claims 52-59 depend from claim 51. Support for claims 52-53 is found on page 5, lines 7-19. Support for claims 54-57 is found on page 8, lines 3-34. Support for claims 58-59 is found on page 11, lines 21-33. Claim 60 is based on claim 13 as filed. Support for claim 60 is found on page 9, lines 6-13. Claims 61-63 depend from claim 60, support for claim 61 is found on page 9, lines 6-13. Support for claims 62-63 is found on page 11, lines 21-33.

The Certified Copy of the Priority Document

The Examiner has indicated that the certified copy of the priority document has not been received. The certified copy of the priority document was filed in the parent U.S. patent application no. 09/902,624 and thus all requirements for a valid priority claim have been met. See e.g. MPEP §201.14(b). Accordingly, in view of the provision of this information by the applicant, it is requested that the Examiner acknowledge that the certified copy of the priority document has been received.

Rejection Under 35 U.S.C. § 112

The Examiner rejected claims 1-20 under 35 U.S.C. §112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant has cancelled claims 1-20 without prejudice to resubmission and has substituted new claims 21-63 therefor.

As to the specific objections of the examiner, the Examiner first takes the position that the specification does not teach how the rules database is updated reflecting the latest publications on the subject. However, the manner of updating the rules database is, in fact, extensively described on page 3, line 31 to page 4, line 18 of the application as originally filed. Specifically, the rules database is updated by a core committee that periodically reviews, on a frequent basis, the latest publications on the subject and decides which adjustments should be made to the rules, based on these latest publications.

As to objection 2 of the examiner, that the specification does not teach how the conferred resistance by substitution is derived and a value is assigned indicative of resistance level, we refer to page 3, line 31 up to page 5, line 11 of the application as originally filed. This section shows that the information on the conferred resistance by substitutions is obtained from scientific articles and evaluations by pharmaceutical companies, which information is carefully examined by the experts and core-committee. In the end the core-committee assigns a value indicating the resistance level (page 4, lines 15-18).

As to objection 3 of the Examiner, the specification, page 5, line 35 up to page 6, line 6 clearly states the confidence levels. The scientific articles upon which the levels will be based will describe whether the drug result is based on suggestive evidence, is proven *in vitro*, or is proven *in*

vivo. Again the core-committee will finally assign the confidence level by reading the scientific articles and determining which of the confidence levels applies.

As to objection 4 of the Examiner, the suitability level is the outcome of the review of all information on resistance level, drug level, confidence level and clinical experience presented to the core-committee and is based upon the knowledge of the expert members of the core-committee and their review of all of this information.

In regard to these objections, the claims do not require specific rules, but only the use of a set of rules having certain characteristics, and these characteristics as such are known to the skilled person. For example as to the suitability level, the claims of the present application are not directed to the specific choice made by the experts of the core-committee, but rather, the claims are directed to the concept of using a suitability level which is, in some way, based on resistance level, drug level, confidence level and clinical experience.

Finally, the Examiner objects to the present claims on the basis that no specific algorithm/steps/procedures are given for derivation of the first, second and third values referred to in the claims. The reason for this is that no specific algorithm/steps/procedures are required for derivation of the first, second and third values, other than that the skilled person take into consideration certain information, as specified in the claims, in deriving those values. The actual derivation process, however, will be carried out by members of a core committee that will exercise their judgment based on the common general knowledge of a skilled person and the information presented to them. Therefore, since the provision of the first, second and third values is carried out by persons using common general knowledge, there is no need for the specification of the present application to disclose, in detail, a specific algorithm/step/procedure for assigning these values. The claims cover any method for assigning these values that involves use of the information specified in the claims, and a skilled person, exercising common general knowledge, is capable of assigning these values without requiring further guidance from the present application.

Applicant respectfully submits that all the claims are now in condition for allowance and requests that the §112, first paragraph rejection be withdrawn.

The Examiner rejected claims 11-13 and 20 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Applicant has cancelled claims11-13 and 20 and has eliminated phrases that the Examiner alleged were unclear or vague in the corresponding new

claims. Applicant respectfully submits that all the claims are now in condition for allowance and requests that the §112, second paragraph rejection be withdrawn.

Rejection Under 35 U.S.C. § 102(b)

The Examiner rejected claims 1, 2, 8, 9, 11 and 16 under 35 U.S.C. § 102(b) as being anticipated by Pazzani *et al.* 'CTSHIV: A Knowledge-Based System For the Management of HIV-infected Patients', Proceedings: Intelligent Information Systems, IIS '97, 1997.

Anticipation under 35 U.S.C. § 102 is established when a single prior art reference discloses, either expressly or under the principles of inherence, each and every element of a claimed invention. See, RCA Corp. v. Applied Digital Data Systems, Inc., 730 F.2d 1440, 1443, 221 U.S.P.Q. 385, 388 (Fed. Cir. 1984), *cert. Dismissed sub nom.*, Hazeltine Corp. v. RCA Corp., 468 U.S. 1228 (1984). The law of anticipation requires that the reference must provide all limitations of the claim. See, Kalman v. Kimberly Clark Corp., 713 F.2d 760, 722, 218 U.S.P.Q. 781, 789 (Fed. Cir. 1983) *cert. denied,* 465 U.S. 1026 (1984) (and overruled in part on another issue) 775 F.2d 1107, 227 U.S.P.Q. 577 (Fed. Cir. 1985).

Applicant has deleted claims 1, 2, 8, 9, 11 and 16 and has substituted new claims 21-63 rendering the Examiner's rejection moot. Applicant submits that the cited reference (Pazzani et al.) fails to provide all the limitations of the new claims 21-63 for at least the reasons given below.

Claims 21-43

Independent claim 21 is based on claim 6 of the application as filed.

Lathrop, R.H. *et al.*, 'Knowledge-Based Avoidance of Drug-Resistant HIV Mutants', American Association of Artificial Intelligence, 1998, pages 1071-1078 (hereinafter "Lathrop '98"), describes an AI system (CTSHIV) that connects the scientific literature describing specific HIV drug resistances directly to the customised treatment strategy of a specific HIV patient. Rules in the CTSHIV knowledge base encode knowledge about sequence mutations in the HIV genome that have been found to result in drug resistance to the HIV virus. The rules represent knowledge about HIV drug resistance as a set of if-then rules of the form:

IF <antecedent> THEN <consequent> [weight]

The system described in Pazzani et al. uses the CTSHIV expert system that is described in Lathrop '98. Lathrop '98 also teaches that, "The weight associated with a rule is not a confidence as in many expert systems. Rather it reflects the estimated level of resistance to a particular drug." (See page 1073, last paragraph of Lathrop '98). Thus, the suitability indication of the rules used in the CTSHIV expert system of Pazzani et al. is not based on at least a combination of a first value indicating the resistance level of the genotype for the drug and a second value indicating the confidence in the first value. Therefore, the subject-matter of claim 21 is novel over Pazzani et al.

Although Lathrop '98 mentions the possibility of basing the rules on a confidence value, it subsequently dissuades the reader from actually basing the rules on a confidence value, as apparently, Lathrop '98 prefers to use only a resistance value. The invention as defined in claim 21 is based on the insight that it is advantageous to include some measure of the confidence in the validity of a rule as well as the level of drug resistance. Thus, according to the invention, the suitability indication of the rules is based on at least a combination of a first value indicating the resistance level of the genotype for the drug and a measure of the confidence in the validity of a rule. This has the advantage that resistance values based on a limited or flawed trial, for instance, do not lead to drugs being disqualified or placed higher in a ranking than warranted. Thus, the physician using the system knows that he is making an informed choice based on accepted practice, rather than, for instance an isolated opinion.

As the prior art leads away from the present invention, and does not mention the possibility of basing a suitability indication of the rules on at least two values or measures, it is submitted that the subject-matter of claim 21 is novel and also non-obvious. Claims 22-43 depend from claim 21 and thus are considered novel and unobvious for at least the same reasons as for claim 21.

Claims 44-50

Claim 44 is based on claims 1 and 9 as originally filed, as well as on page 10, lines 21-22 of the description as filed.

Lathrop '98, describes an AI system (CTSHIV) that connects the scientific literature describing specific HIV drug resistances directly to the customised treatment strategy of a specific HIV patient. Rules in the CTSHIV knowledge base encode knowledge about sequence mutations in the HIV genome that have been found to result in drug resistance to the HIV virus. The possible combination drug-treatment regimens currently approved by the U.S. Food and Drug

Administration are considered and ranked by their estimated ability to avoid identified current and nearby drug-resistant mutants. CTSHIV ranks alternative drug combinations using the current resistance weight and the nearby mutant resistances. The final result of application processing is to recommend the five highest-ranked combinations of one, two, three and four drugs.

Thus, the known method does not comprise individually ranking the drugs suitable for therapy displaying the individual drugs suitable for therapy in a ranking in accordance with their suitability indication, and wherein certain combinations of drugs are displayed in the ranking along with the individual drugs according to the suitability indication for the combination. Specifically, only combinations of drugs wherein the suitability ranking is altered because one or both of the drugs influence(s) the suitability indication of the other drug, are listed in the ranking of individual drugs.

Pazzani et al. also does not display a ranking which includes both the individual drugs and certain combinations of drugs displayed together. Rather, Pazzani et al. uses the standard system of Lathrop '98. Thus, the method of Pazzani et al. only takes account of resistance to drugs or combinations of drugs. However, a choice of drug also has other effects, which a physician would take into account when deciding on a drug regimen. Thus, a combination might come out better than would be suggested by a method based on drug resistance alone. It is therefore advantageous to only rank combinations of two or more drugs where drugs in the combination influence each other's suitability indication.

The method of claim 44 has the advantage of providing more flexibility to the physician in making an informed decision for a therapy. Additionally, the method can be implemented on a computer more efficiently, as it is not necessary to evaluate all possible combinations.

It is observed that none of the cited prior art publications (all relating to CTSHIV) provide a suggestion, motivation or incentive to modify the known system in a direction making it suitable for use in a method as defined in claim 44. In particular, Pazzani *et al.* 'CTSHIV : A Knowledge-Based System For the Management of HIV-infected Patients', Proceedings: Intelligent Information Systems, IIS '97, 1997, pages 7-13, states that (page 8, right-hand column, lines 32-36) 'a branch-and-bound search is used to find the five best combinations of 2 drugs, the five best combinations of 3 drugs and the five best combinations of 4 drugs.' Thus, the prior art teaches away from the present invention. In particular, the prior art does not consider that factors other than resistance to drugs or combinations of drugs might affect the combination that should be chosen.

Thus, it is submitted that the subject-matter of claim 44 is both novel and non-obvious over the prior art. Claims 45-50 all depend from claim 44 and thus are considered patentable for at least the same reasons as claim 44.

Claims 51-59

Claim 51 corresponds to claim 2 as filed.

Lathrop '98, describes an AI system (CTSHIV) that connects the scientific literature describing specific HIV drug resistances directly to the customised treatment strategy of a specific HIV patient. Rules in the CTSHIV knowledge base encode knowledge about sequence mutations in the HIV genome that have been found to result in drug resistance to the HIV virus. The possible combination drug-treatment regimens currently approved by the U.S. Food and Drug Administration are considered and ranked by their estimated ability to avoid identified current and nearby drug-resistant mutants. The system accepts as input experimentally determined HIV sequences extracted from the patient (see also Figure 4). An important limitation to the approach taken by the authors of that article is (page 20, section 'Limitations') that 'sequence-based rules capture only part of the domain knowledge about drug-resistance.'

From the quoted passage and the examples of rules given in the article it is clear that the rules in CTSHIV are not based on at least a first value indicating the resistance level of the genotype for the drug when present at a certain drug level in a patient. Thus, the subject-matter of claim 51 is novel. The same logic applies to Pazzani et al.

The prior art cited does not contain a suggestion to modify the described system in the direction of claim 51 either. In fact, the drug level is not even mentioned as affecting the suitability of a drug, through the degree of resistance, through side effects or in any other way. As the invention according to claim 51 does allow such effects to be taken into account in determining the suitability of a drug for a certain genotype, it provides output of a better quality than the known method.

Thus, it is submitted that the subject-matter of claim 51 is also non-obvious. Claims 52-59 all depend from claim 51 and thus are considered to be novel and unobvious for at least the same reasons as given for claim 51.

Claims 60-71

Claim 60 is based on claim 13 as filed.

Lathrop '98, describes an AI system (CTSHIV) that connects the scientific literature describing specific HIV drug resistances directly to the customized treatment strategy of a specific HIV patient. Rules in the CTSHIV knowledge base encode knowledge about sequence mutations in the HIV genome that have been found to result in drug resistance to the HIV virus. The possible combination drug-treatment regimens currently approved by the U.S. Food and Drug Administration are considered and ranked by their estimated ability to avoid identified current and nearby drug-resistant mutants. The system accepts as input experimentally determined HIV sequences extracted from the patient (see also Figure 4). An important limitation to the approach taken by the authors of that article is (page 20, section 'Limitations') that 'sequence-based rules capture only part of the domain knowledge about drug-resistance.'

As no information is given about any other information that is entered or used to select a suitable drug therapy, the use of the clade of a virus in selecting a suitable drug therapy is not disclosed in Lathrop '98. Also, Pazzani et al. does not disclose the use of the clade of a virus in selecting a suitable drug therapy.

It is known that viruses with different clades exhibit different patterns of resistance. This is the result of the evolutionary history of particular strains of the virus. More importantly, many reports of research into drug effectiveness compare the drug's effectiveness in viruses of different clades. The invention as defined in claim 60 enables such research reports to be taken into account, thus improving the knowledge base on which the rankings are based.

The effect of a virus's clade on its suitability for therapy is not disclosed in any of the cited publications. No suggestion is given to also include information relating drugs' suitability to viral clades in a database used in a method for effecting computer-implemented decision support. For this reason, it is submitted that the subject-matter of claim 60 is both novel and non-obvious. Claims 61-71 all depend from claim 60 and thus are considered patentable for at least the same reasons as given for claim 60.

In view of the fact that Pazzani et al. lacks a teaching or suggestion of certain elements of the present claims, applicant respectfully submits that all the claims are now in condition for allowance and requests that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, it is believed that this application has been placed in condition for allowance. An early action to that effect is cordially requested.

The Commissioner is hereby authorized to charge any additional fees, which may be required for this Response, or credit any over payment to Deposit Account No. 50-0462.

In the event that an extension of time is required, or may be required, the Commissioner is hereby requested to grant a petition for that extension of which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-0462.

Respectfully Submitted,
Knoble & Yoshida, LLC

November 26, 2003

Kevin J. Dunleavy
Reg. No. 32,024

Knoble & Yoshida, LLC (Customer No.: 21,302)
Eight Penn Center
Suite 1350
1628 John F Kennedy Blvd.
Philadelphia, PA 19103
Tel. (215) 599-0600
Fax (215) 599-0601
www.patentwise.com